REMARKS

Of the thirty-nine claims currently pending in the present application, sixteen of them, Claims 3-6, 12-15, 21-24 and 32-35, have been withdrawn from consideration. The remaining twenty-six claims, Claims 1, 2, 7-11, 16-20, 25-31 and 36-39, examined on the merits in this application, have been objected to and rejected on formal and/or substantive grounds. Applicants have amended their claims and respectfully submit that all the claims currently in this application are patentable over the objection and rejections of record.

Turning first to the objections of record, several of the claims incorporate improper Markush terminology. The claims of the present application have been amended to introduce proper Markush language in the claims where such groupings are set forth. Thus, all claims which recite a Markush group recite the phrase --selected from the group consisting of--. The original language which utilized other phraseology has been removed. It is also noted that in reciting subscripts improper Markush group language has been replaced with acceptable claim language.

The second objection is directed to Claim 30 which recites an independent pharmaceutical composition claim which depends from Claim 1, a method claim.

Applicants have amended Claim 30 by deleting it and replacing it with new independent Claim 44 which recites the same limitations as Claim 30 without dependency from Claim 1 which is not directed to a composition.

In addition to the amendment of the claims based on the aforementioned objections, applicants have amended their claims to correct the improper recitation of subscripts. In addition, certain Markush groups recite halogen radicals incorrectly. Both of these classes of improper recitations have been corrected.

Claims 11, 16-20 and 25-27 stand rejected, under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, Claims 11 and 19 are deemed indefinite because these claims, which recite methods of treating or preventing stasis in the stomach, are drawn to distinct methods of treating gastrointestinal disorders independent of whether status results from hypomotility. As such, the Official Action submits that it is improper for Claims 11 and 19 to depend from Claim 1.

Applicants have removed any indefiniteness from Claims 11 and 19 and the claims that depend therefrom. This has been accomplished by redrafting dependent Claims 11 and 19 as new independent Claims 42 and 43, respectively.

New independent Claims 42 and 43 recite the methods of Claims 11 and 19, respectively, but instead of referring to Formula (IA) or (IB), as set forth in Claim 1, recite the definitions of these formulae as set forth in these new independent claims. As such, there can be no question of the definitiveness of new independent Claims 42 and 43 which predicated the original rejection of Claims 11 and 19, which these claims respectively replace.

It is noted that new independent Claim 43 includes the term "morphine-like" which is deemed a separate ground of indefiniteness predicating rejection of that claim and the claims dependent therefrom.

Applicants have retained the term "morphine-like" insofar as its meaning is well known to those skilled in the art. That term means compounds other than morphine that act in an analogous manner and have the basic morphine structural formula. In view of the many compounds that are "morphine-like," it would be duly limiting to require a recitation of the multiplicity of compounds that fit this description. Those skilled in the art are well aware of

the meaning of a "morphine-like" compound. As such, the test of definitiveness, that those skilled in the art understand the metes and bounds of that recitation, is met.

Four substantive grounds of rejection are imposed in the outstanding Official Action. The first of these grounds of rejection is directed to Claims 30, 31 and 36-39. These claims stand rejected, under 35 U.S.C. §102(b), as being anticipated by International Publication No. WO 97/42174 to Pfizer Inc.

The Official Action states that Pfizer discloses pharmaceutical compositions, for administration to humans, containing effective amounts of the compounds embraced by Formula (I), with a preferred compound being cis-4-cyano-4-(1-(cyclohexyl-3-ethyl)-1H-indazol-6-yl)-cycloxhexanecarboxylic acid.

The Official Action emphasizes that the intended use of the composition to treat or prevent stasis in the stomach must result in a structural difference between the claimed composition and compositions of the prior art in order to patentably distinguish the claimed invention from the prior art. The Official Action states that if the prior art structure is capable of performing the intended use then it meets the claim. The Official Action concludes that since the disclosed pharmaceutical compositions of Pfizer contain effective amounts of the pharmaceutical composition claimed by applicants, that establishes that Claims 30, 31 and 36-39, all the claims currently in this application directed to a pharmaceutical composition, are anticipated by Pfizer.

Applicants respectfully submit that in order for a reference to anticipate a claim that reference must disclose each and every limitation of the rejected claim. Applicants submit that Pfizer does not anticipate all the limitations of any of the pharmaceutical composition claims subject to this ground of rejection.

All that is necessary to establish novelty of the claims subject to this ground of rejection is to analyze new independent Claim 44, which, as stated above, represents Claim 30 rewritten in independent form. Claim 44 requires that the pharmaceutical composition be present in an amount sufficient to restore normal motility to a patient suffering from stasis in the stomach. Even if the pharmaceutical composition in Pfizer were identical to the pharmaceutical composition of Claim 54, from which Claims 31 and 36-39 ultimately depend, still that limitation is not disclosed in Pfizer.

In Pfizer a substituted indazole derivative pharmaceutical composition is disclosed for inhibition of phosphodiesterase type IV (PDE4) and the production of tumor necrosis factor in a mammal. As stated in the specification of the present application at Page 1, lines 15-22, although the therapeutic compounds useful as active agents in the pharmaceutical compositions are closely related to the inhibitors of Pfizer, the art has incorrectly taught that PDE4 inhibitors antagonize gastrointestinal contractile responses, suggesting their use as antikinetic agents for treating hypermotility disorders. Rather, the therapeutic agents of the present application are prokinetic agents for treating gastric hypomotility, as surprisingly discovered in the invention of the present application.

This fundamental distinction emphasizes the totally distinct biological activity of the claimed compositions compared to the activity of the pharmaceutical compositions of Pfizer. That is, the concentrations of the pharmaceutical compositions, given the distinct and different biological pathways for the effectiveness of these compositions, emphasize that no inherency can be presumed since the above remarks provide no basis for the conclusion that the concentration of composition utilized in the Pfizer disclosure overlaps that of an effective amount of a claimed pharmaceutical composition of the present application.

The Official Action, appreciating this deficiency in the applied reference, recites concentrations set forth in the specification of the present application. The Official Action makes no such reference to any concentration range recited in Pfizer. This is reasonable insofar as Pfizer does not provide any specific concentration ranges. Rather, the Pfizer disclosure merely describes an effective amount to inhibit PDE4 for the production of tumor necrosis factor in a mammal. This "effective therapeutic amount" cannot be presumed to overlap that of the effective amount necessary for a composition utilized in the treatment or the prevention of stasis in the stomach of a patient insofar as the treatment of the two separate and distinct classes of diseases are effectively treated by the same pharmaceutical composition in far different ways.

The second novelty rejection is directed to Claims 11, 16-20 and 25-27. These claims stand rejected, under 35 U.S.C. §102(b), as being anticipated by Pfizer.

The Official Action states that Pfizer discloses methods of treating various gastrointestinal disorders, such as Crohn's disease, ulcerative colitis and inflammatory bowel disease, wherein the method comprises administering pharmaceutical compositions containing effective amounts of the compounds embraced by Formula I.

Again, the Official Action argues that the Pfizer compounds embrace identical compounds to those utilized in the rejected claims. As such, Claim 11, which has been redrafted in independent form as new Claim 42, as well as Claims 16 to 20 and 25 to 27, which all ultimately depend from original Claim 11, are anticipated by the Pfizer disclosure.

The above remarks, directed to the anticipation of the pharmaceutical composition claims, provide but one ground in support of the proposition that none of these claims are anticipated by Pfizer. As stated above, the biological pathway for effectiveness of the

prevention of stasis in the stomach of a patient, which results in the conditions recited in original Claim 11, as well as new Claim 42, do not employ the same concentrations of the active compounds as those required to cure the conditions that are treated in the Pfizer prior art reference.

Applicants appreciate that if a different disease were treated in a concentration equivalent to or overlapping the range which is claimed that claim would be anticipated based on inherency. However, the aforementioned remarks, in support of the proposition that different effective amounts are required for the totally distinct class of diseases treated by the respective disclosures, eliminate any basis for holding such claims inherently anticipated.

Applicants strongly urge that there is a critical criterion for the imposition of an anticipation rejection predicated upon inherency not considered in the Official Action. That is, when a reference is silent about an asserted inherent characteristic such gap in the reference must be filled by intrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the applied reference. This is so insofar as inherency may not be established by probabilities or possibilities. Continental Can Co. USA, Inc. v. Monsanto., 974 F.2d 1264, 1268-1269, 20 USPQ2d 1746, 1749 (Fed. Cir, 1991). Here, no such evidence is proffered.

The Official Action appreciates this distinction insofar as it attempts to recite diseases, among the many disclosed at Page 10 of Pfizer, that focus on the digestive system. However, none of these conditions, Crohn's disease, ulcerative colitis or inflammatory bowel disease, are among the diseases that are treated in accordance with the claims subject to this ground of rejection. Obviously, the other diseases recited in Pfizer, which run the gamut of asthma to arthritis to AIDS, are totally distinct from the diseases subject to treatment in the method

claims subject to this ground of rejection. That the treatment of gastrointestinal disorders are different from the conditions treated in the Pfizer disclosure establishes the requirement of providing intrinsic evidence.

The third substantive ground of rejection is directed to Claims 1, 2 and 7-10. These claims stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Pfizer in view of U.S. Patent 5,891,904 to Stief et al.

The Official Action avers that Pfizer discloses methods of treating various gastrointestinal disorders, such as Crohn's disease, ulcerative colitis and inflammatory bowel disease, wherein the method comprises administering pharmaceutical compositions containing effective amounts of the compounds embraced by Formula I. The Official Action, however, admits that Pfizer does not disclose a method which is effective in treating stasis resulting from hypomotility in the stomach. Therefore, the Stief et al. patent is applied for its disclosure that the use of pharmaceutical compositions containing PDE4 inhibitors modulate the motility or peristalsis of the gastrointestinal tract. The Official Action states that PDE4 inhibitors may be used to treat irritable colon or stomach cramps. Thus, the Official Action concludes that it would be obvious to one of ordinary skill in the art to modify the methods of Pfizer to treat or prevent stasis in the stomach because PDE4 inhibitors are capable of modulating motility and perilastais of the gastrointestinal tract.

Applicants emphasize that the inhibitors disclosed in Stief et al. are totally distinguished and different from the PDE4 inhibitors of Pfizer. Therefore, there is no scientific basis upon which the two references can be combined to make obvious the claims of the present application. In view of the fact that the principal Pfizer reference, which employs PDE4 inhibitors, does not teach treatment or prevention of gastric or gastrointestinal

disorders, it is apparent that the combined teaching of these references does not make this teaching.

Suffice it to say, when two references are combined there must be motivation suggested in the references for combining their teachings. That Pfizer and Stief et al. are directed to totally different and distinct diseases, utilizing different compounds in different methods of treatment, the combination of the two applied references is nothing more than a hindsight appreciation of the teaching of the present application.

Even if the PDE4 inhibitors taught in Stief et al. were effective in the treatment of hypomotility in the gastrointestinal tract, which is not conceded, there is no teaching in Stief et al. of utilization any of the claimed compounds, e.g. the compounds of Formula IA and IB, in the prevention or treatment of gastric or gastrointestinal disorders. This is especially the case insofar as inaccuracies associated with the use of PDE4 inhibitors in the prior art, as summarized in the specification at Page 10, line 18 to Page 11, line 6, would bar such use. That portion of the specification establishes that not all PDE4 inhibitors prevent stasis of the stomach in a patient. Certainly, there is no disclosure in Stief et al. establishing that any of the PDE4 inhibitors of that disclosure, which are clearly distinguished from those claimed in the present application and those described in Pfizer, prevent stasis in the stomach of a patient.

The final ground of rejection is directed to Claims 28 and 29. Claims 28 and 29 stand rejected, under 35 U.S.C. §103(a), as being unpatentable over Pfizer in view of Stief et al. and taken in further view of U.S. Patent 5,820,583 to Demopulos et al.

Claim 28 sets forth ten classes of a second therapeutic agent which may be co-administered with the compound employed in Claim 1. Claim 29 recites specific classes of

compounds and polypeptide agents within the contemplation of the generic classes set forth in Claim 28. The tertiary Demopulos et al. reference is applied for its disclosure of DAMGO, a known opioid analogesic which induces anti-nosciceptive effects, insofar as the Official Action, by application of Demopulos et al., admits that Claims 28 and 29 are not made obvious by the teaching of Pfizer in view of Stief et al.

Applicants acknowledge that Demopulos et al. discloses that DAMGO is a known opioid receptor agonist. However, the disclosure of this agent in a disclosure directed to a method of inhibiting pain and inflammation at a wound during a surgical procedure does not make obvious the method of Claims 28 and 29, directed as these claims are to a method of treating or preventing stasis in the stomach of a patient.

The above remarks establish that none of the substantive grounds of rejection can be sustained. Therefore, reconsideration and removal of these grounds of rejection is deemed appropriate. Such action is respectfully urged.

The Abstract of the Disclosure has been objected to as containing two paragraphs and in excess of 150 words. Applicants have replaced the original Abstract of the Disclosure with a new Abstract of the Disclosure submitted herewith. That Abstract is one paragraph and is clear and concise, containing less than 150 words. As such, the objection to the Abstract has been overcome with its amended replacement.

Applicants have amended the specification to include the sequence listing that is separately submitted as a Statement under C.F.R. §1.821. Applicants by this amendment meet the requirement of submitting a separate copy of the sequence listing. The specification, specifically the paragraph at Page 59, line 29 to Page 61, line 22, has also been amended to

add the sequence numbers of the nucleotide and/or amino acid sequences summarized on the newly added sequence listing.

The above amendment and remarks establish the patentable nature of all the claims examined on the merits in this application. Notice of Allowance and passage to issue of these claims, Claims 1, 2, 7-10, 16-18, 20, 25-29, 31, 36-39 and 42-44, is respectfully solicited.

Respectfully submitted,

Marvin Bressler
Registration No. 25,132
Attorney for Applicants

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
516-742-4343
MB:ml